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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/533,750	12/05/2005	Yoichi Matsubara	10939/2192	5376

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EXAMINER	
SAJJADI, FEREYDOUN GHOTB	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 04/21/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/533,750	MATSUBARA ET AL.	
	Examiner	Art Unit	
	Fereydoun G. Sajjadi	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-6* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 May 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This action is in response to papers filed December 30, 2005. Currently, claims 1-6 are pending in the application, and are under examination.

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is unclear. Claim 1 recites: "A method of detecting a base sequence, comprising the steps of: amplifying DNA containing a target base sequence to be detected having a mutation site" in the first and second lines of the claim. A base sequence and a target base sequence are single base nucleotides. As such they may be considered point mutations. It is therefore not clear what is meant by having a mutation site in the context of said single base. Claims 2 and 3 depend from claim 1.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3, 4 and 6 are rejected under 35 USC 103(a) as being unpatentable over Lay et al. (Clin. Chem. 43(12):2262-2267; 1997), in view of Klepp et al. (Biochemica 2:14-16; 2000).

Claim 1 is drawn to a method of detecting a base sequence, comprising the steps of: amplifying DNA containing a target base sequence to be detected having a mutation site using DNA polymerase; hybridizing the amplified DNA to a hybridization probe having a base sequence complementary to the target base sequence to be detected; and detecting a hybrid formed by the hybridization, wherein at least one of primers to be used in the DNA amplification is labeled with a first labeling agent so that the amplified DNA will be labeled with the first labeling agent, the hybridization probe is labeled with a second labeling agent and contained in a reaction solution for effecting the DNA amplification, the base sequence of the hybridization probe is designed not to inhibit the DNA amplification, and the hybrid is detected by affinity chromatography with the use of the first and second labeling agents.

Claim 3 is directed to the method according to claim 1 or 2, wherein the DNA amplification is carried out by PCR.

Claim 4 is drawn to a kit comprising: primers for amplifying DNA containing a target base sequence to be detected having a mutation site using DNA polymerase; a hybridization probe having a base sequence complementary to the target base sequence to be detected; and a test strip for affinity chromatography, wherein at least one of the primers to be used in the DNA amplification is labeled with a first labeling agent so that the amplified DNA will be labeled with the first labeling agent, the hybridization probe is labeled with a second labeling agent, the base sequence of the hybridization probe is desired not to inhibit the DNA amplification, and the test strip allows of detection of a hybrid of the amplified DNA and the hybridization probe with the use of the first and second labeling agents.

Claim 6 is directed to a kit according to claim 4 or 5, wherein the primers are primers for PCR.

The term kit is not given any patentable weight, as it is directed to a composition.

Lay et al. describe a single-step method for detecting a factor V Leiden single point mutation using rapid-cycle PCR and simultaneous analysis, by using an amplification primer labeled with Cy5 (a first labeling agent) in the presence of a 3'-fluorescein-labeled probe (second labeling agent) that covers the mutation site and hence complementary to the target sequence (Abstract). Lay et al. do not describe the detection of the hybrid by affinity chromatograph, as their approach utilizes FRET technology.

Klepp describes a DNA detection test strip for the rapid detection of labeled PCR products. Specifically described are 5'-end labeled PCR primers that may be pre-labeled with dioxigenin (first column, p. 14). Klepp additionally states: "In cases where a labeled primer and a labeled oligonucleotide (hybridization probe) are used together in a PCR, verify that the primer and oligonucleotide do not hybridize to each other." (second column, p. 14). Therefore, teaching that the oligonucleotide sequence (hybridization probe) should be designed not to inhibit the DNA amplification. Klepp further describe a biotinylated hybridization probe (second column, p. 15) and the details of the chromatographic test strip containing anti-DIG-gold conjugate and streptavidin for detection of the first and second labeling agents (second column, p. 14 and first column, p. 15).

The methods described by both Lay et al. and Klepp et al. are directed to the PCR amplification and detection of sequences using differentially labeled primer and hybridization probes. However, the method of Lay et al. requires the use of specialized instruments such as a fluorometer and fluorescent labeled probes. Thus a person of ordinary skill in the art without access to specialized instruments such as costly fluorometers would be motivated to combine the point mutation detection method of Lay et al. and the test strip affinity chromatographic method of Klepp, to rapidly detect a point mutation following amplification and hybridization, with lower expense in a clinical setting.

Therefore, it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to utilize the combination of the point mutation detection method of Lay et al. and the test strip affinity chromatographic method of Klepp, resulting in the practice of the instantly claimed invention. A

person of ordinary skill in the art, would have been motivated to combine the elements of differentially labeled PCR primer and hybridization probe, together with the detection method utilizing affinity chromatography test strip, (as outlined in the preceding section), and would have a reasonable expectation of success in detecting a mutation site in a sequence, because the PCR mediated amplification of a target sequence and specific detection of a mutation site are enabled by the procedures described by Lay et al. and Klepp. Moreover, each limitation contained in the composition (kit) of claim 4 is effectively described by the teachings of Lay et al. and Klepp.

Claims 2 and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lay et al. and Klepp as applied to claims 1, 3, 4 and 6 above, and further in view of Gunneberg et al. (Clin. Chem. 39(10):2157-2162; 1993).

Claim 2 is drawn to the method according to claim 1, wherein the mutation site is a point mutation, and the reaction solution for effecting the DNA amplification further contains an unlabeled oligonucleotide having a base sequence different in a single base at the position of the point mutation from the base sequence of the labeled hybridization probe, in an amount sufficient to enhance the specificity of hybridization of the amplified DNA to the hybridization probe.

Claim 5 is directed to the kit according to claim 4, wherein the mutation site is a point mutation and the kit further comprises an unlabeled oligonucleotide having a base sequence different in a single base at the position of the point mutation from the base sequence of the labeled hybridization probe.

Neither Lay et al. nor Klepp teach the inclusion of an unlabeled oligonucleotide having a base sequence different in a single base at the position of the point mutation from the base sequence of the labeled hybridization probe. Gunneberg et al. describe a competitive assay to improve the specificity of detection of single-point mutations (Title). Specifically described are a normal allele referred to as M, and a single-point mutation referred to as Z, and mixed amplified products containing M and Z alleles of a polymerase chain reaction incubated with a two fold molar excess of unlabeled

oligonucleotide, wherein the products were incubated with unlabeled M-specific oligonucleotide, followed by hybridization with radiolabeled Z-specific oligonucleotide, an *vice versa*, in an assay that increased the specificity of single-point mutation detection three to four fold.

The methods described by Lay et al. and Klepp et al. and Gunneberg et al. are directed to the PCR amplification and single point mutation detection of sequences. A person of ordinary skill in the art would have been motivated to combine the differentially labeled point mutation PCR reaction method of Lay et al., and the test strip affinity chromatographic detection method of Klepp, with the hybridization specificity enhancing method of Gunneberg et al. to reduce false positive signals and detect the point mutation of interest with greater specificity.

Therefore, it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to utilize the combination of the point mutation detection method of Lay et al., the point-mutation enhancing method of Gunneberg et al. and the test strip affinity chromatographic method of Klepp, resulting in the practice of the instantly claimed invention. A person of ordinary skill in the art, would have been motivated to combine the elements of differentially labeled PCR primer and hybridization probe, and the hybridization specificity enhancing method together with the detection method utilizing affinity chromatography test strip, and would have a reasonable expectation of success in detecting a point mutation, because the PCR mediated amplification of a target sequence and specific detection of a mutation site are complementary procedures described by Lay et al., Gunneberg et al. and Klepp. Moreover, each limitation contained in the composition (kit) of claim 5 is effectively described by the teachings of Lay et al., Gunneberg et al. and Klepp.

Hence, the claimed invention a whole is *prima facie* obvious, absent evidence to the contrary.

Conclusion

No claims are allowable.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Any inquiry concerning this communication or earlier communications regarding the formalities should be directed to Patent Analyst William Phillips, whose telephone number is **(571) 272-0548**.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fereydoun G. Sajjadi whose telephone number is **(571) 272-3311**. The examiner can normally be reached Monday through Friday, between 7:00 am-4:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave T. Nguyen can be reached on **(571) 272-0731**. The fax phone number for the organization where this application or proceeding is assigned is **(571) 273-8300**. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free).

For all other customer support, please call the USPTO Call Center (UCC) at **(800) 786-9199**.

Q. JANICE LI, M.D.
PRIMARY EXAMINER

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